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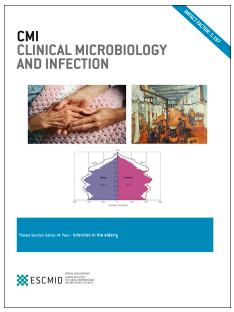

Accelerating clinical trial implementation in the context of the COVID-19 pandemic: challenges, lessons learned and recommendations from DisCoVeRy and the EU-SolidAct EU response group

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Accelerating clinical trial implementation in the context of the COVID-19 pandemic: Challenges, lessons learned and recommendations from DisCoVeRy and the EU-SolidAct EU Response group

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The spread of SARS-CoV-2 has triggered new approaches in clinical research. These include the conduct of adaptive platform trials, such as RECOVERY[1], REMAP-CAP and DisCoVeRy[2]. Platform trials allow the study of several target treatments in the same disease context on a perpetual basis, with therapies being allowed to enter or leave the platform based on a decision algorithm [3]. DisCoVeRy is part of a European project, EU-RESPONSE, originally set up in France as a WHO Solidarity trial add-on study [4]. EU-RESPONSE is funded by the Horizon 2020 programme to allow the expansion of DisCoVeRy to other European/associated countries, and the launch of "EU-SolidAct", a second-generation pan-European platform trial for COVID-19/emerging infectious diseases, implemented to extend what was initiated by DisCoVeRy. These trials have faced multiple hurdles.

Regulatory hurdles

Under the 2001/20/EC Directive, approval of multinational clinical trials in Europe requires parallel and independent submissions to the national competent authority (NCA) and ethics committee (EC) of each participating country. Since 2009, the European Medicines Agencies has developed a Voluntary Harmonisation Procedure (VHP) whereby a single application is sent to one reference NCA coordinating the response of all NCAs, before a national phase takes place in each country. Some member states offer the involvement of Ethics Committees (VHP plus process).

Whereas DisCoVeRy used multiple national applications (VHP not possible because the trial received initial approval in France), EU-SolidAct opted for the VHP.

In DisCoVeRy, five countries were involved at the onset of the pandemic, in 2020. The median review time was 13 days (IQR 7-17) and 17 days (IQR 15-21) for NCAs and ECs, respectively. In 2021, the new treatment arm required the submission of an amendment that applied to the countries already involved, but also to the 8 countries that had started recruiting since the first approval. The median amendments review time was 47.5 days (IQR 34.25-63.5) for 10 of the 13 countries and 35.5 days (IQR 27.75-58.5) for 8 of the 13 countries, for NCAs and ECs, respectively. The shorter timeframe observed in 2020 is related to the fast-track procedure implemented for all of these countries at the beginning of the pandemic. The fast-track procedure was withdrawn in 2021. Duplicate reviews of the protocol with similar questions/queries were in particular requested from various countries.

For EU-SolidAct, the VHP and VHP+ assessment took 56 days. However, the duration of the subsequent national phase varied from a few days to several months. The median review time was 20.5 days (IQR 12.5-43.5) for 14 of the 16 countries and 35 days (IQR 29-42) for 9 of the 16 countries, for NCAs and ECs, respectively. The timeframe for substantial amendments, including adding a new arm, is expected to be 50 days.

The aim of these clinical trials is to urgently obtain clinically relevant results and propose therapeutic and preventive solutions. Prolonged evaluation times are therefore obstacles to finding these solutions and to the subsequent rapid development of best clinical care for patients.

In comparison, in the UK, where the conduct of clinical trials seems to have been more successful, with the support of the competent authorities, COVID-19 studies were swiftly revised to accelerate the approval process during the health crisis. The National Institute for Health Research (NIHR) established a single UK-wide process to prioritise COVID-19 research as Urgent Public Health (UPH) Research early in the pandemic [5-6-7]. This enabled the implementation of a fast-track review or process by offering

reviews by the Research Ethics Committee and NCA with the submission of one application reviewed and the issue of approval within days.

There were challenges in drafting the information leaflet as well. The adaptation of each leaflet to local regulations, including the size of the document and the number of consents to be drafted per party required by ethics committees, led to numerous exchanges and submission extensions.

Some hurdles are expected to be reduced with the new Regulation 536/2014 on clinical trials, which is to come into force in January 2022 (see appendix 1). This regulation will ensure that rules for conducting clinical trials are identical throughout the EU and will also allow a coordinated assessment of clinical trial applications and especially the protocol and the product between Member States [8-9].

Nevertheless, it seems that the coordinated process under this regulation will not apply to all the steps of approval. For example, it will not apply to patient information and consent, which will continue to be dealt with at the site level. We therefore suggest the following considerations when implementing this legislation:

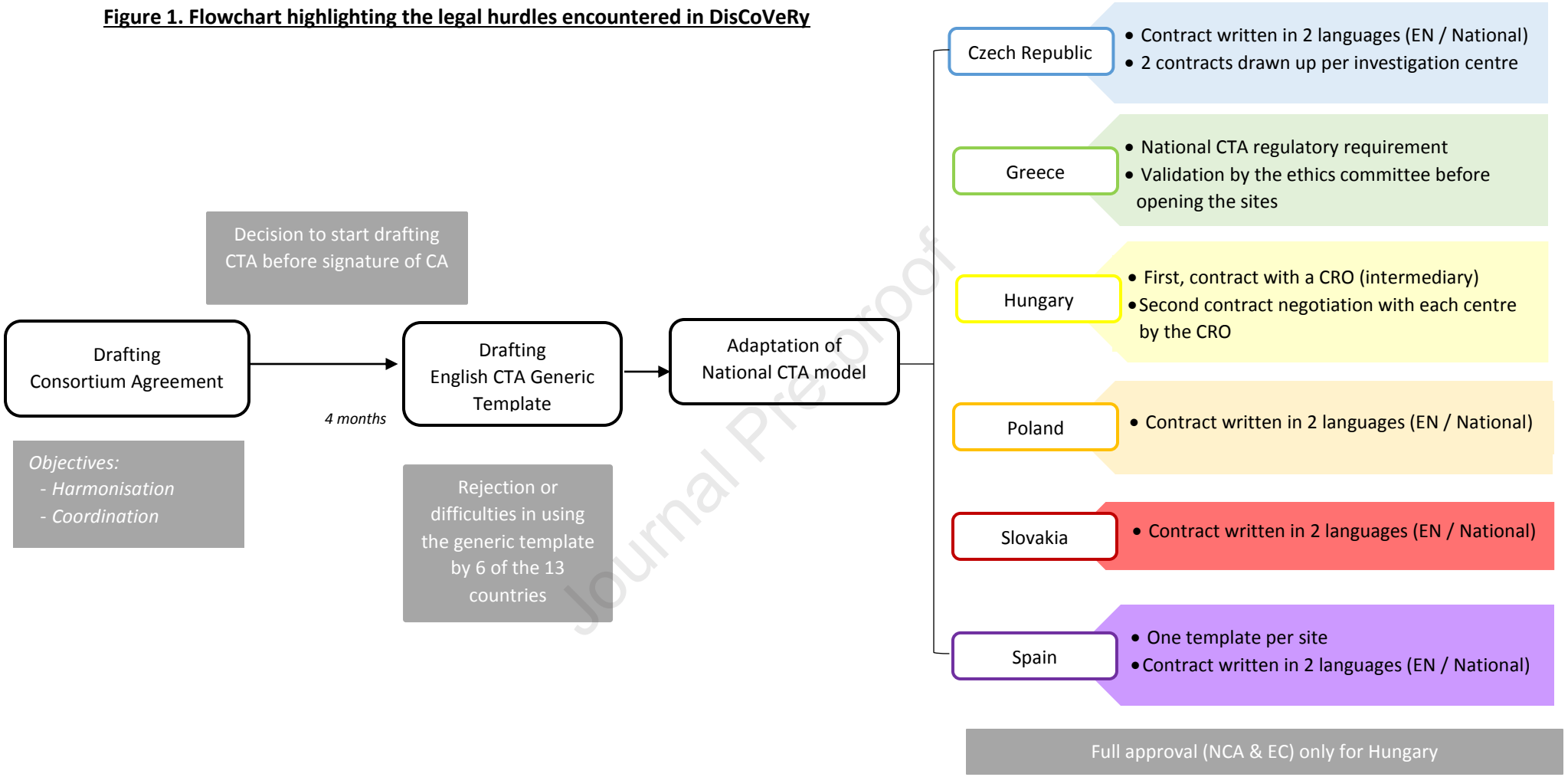
- *For EU-funded platform trials during the pandemic, to reach a single decision the assessment involving NCAs and ECs must be mandatory for all Member States*
- *A protocol pre-submission review involving all relevant NCAs/ethics committees, to discuss potential grounds for non-approval early on.*
- *During the health crisis, enabling the implementation of a fast-track process by offering review by a research ethics committee and an NCA, with submission of one application reviewed within 1 week.*
- *Amendments must be subject to fast-track review.*
- *Repurposing trials testing drugs with known safety profiles should be seen as low-risk trials, with shorter timelines. The definition of 'low intervention trials' under Regulation 536/2014 must include such trials.*

Here, we have focused on inpatient studies. One should acknowledge that outpatient trials in which the logistics are challenging (eg, test turnaround time, contacting people with a positive test, quarantine limiting study visits, etc) will be even more difficult to implement if national rules continue to be defined without any EU harmonisation and without taking the need for trials into account.

Legal hurdles

Negotiations of agreements between the trial sponsor and sites, and translations into local languages, represent a major bottleneck. Some sites insist on using their own templates, which requires valuable time and resources in order to understand regional legislation and its legal language. The flowchart below illustrates these hurdles.

Figure 1. Flowchart highlighting the legal hurdles encountered in DisCoVeRy



Acronyms

CA: Consortium Agreement
CTA: Clinical Trial Agreement
CRO: Contract Research Organisation
EN: English

Following this we suggest:

- *Development of a pan-European site agreement template by the EC, which allows an electronic signature for all parties, and translated into all European languages.*

Acceptance of this template by implementing sites/institutions could be an eligibility criterion for publicly funded multinational trials in the EU.

- Mention on the information sheet of the sharing of individual participants' data byEU Member States participating in the trial for public health benefits.

Financial hurdles

Immediate availability of sufficient funding is critical for the success of multinational trials in a pandemic.

This pandemic has demonstrated that implementing an EU seed grant programme is critical when sponsored funding is not yet available, but the problem demands immediate investigation[(10)]. The substantial and ambitious seed grant will allow the research to start quickly.

Bottom-up funding mechanisms based on competitive calls are too slow, and have resulted in duplication and fragmentation of trials. We propose:

- *A top-down decision mechanism established at EU level that promptly releases appropriate budgets, using funding mechanisms from the Horizon Europe budget and/or ERA4Health in coordination with the European Health Emergency Preparedness and Response Authority (HERA).*
- *Subsequent funding of intervention arms from the same public sources, with levels of funding adapted to the nature of the trial.*
- *Safeguards to ensure public health relevance, independence and scientific excellence.*

Conclusion

Europe, despite its diversity, must be capable of responding unanimously and rapidly to any health crisis; establishing effective medical collaboration is key to responding to epidemics/pandemics. Regulatory, legal and financial hurdles have significantly slowed down efficient conduct of clinical trials, which is unacceptable during a raging pandemic. Adaptative, large clinical trials during pandemics should be considered a critical countermeasure, and the pace of regulatory approval should be consistent with the urgency of this situation. This is also applicable to non-emergencies and to multicentre clinical trials in general. There is a definite need to overcome these hurdles to prepare Europe for the next pandemic and to make United Europe of Research a reality.

Appendix

Summary of key changes from Directive to Regulation and Authors' inputs.

Directive 2001 / 20 (Currently in use)	CT Regulation (Upcoming application)	Authors' inputs for
• No Low-intervention CT	• Low-intervention CT with adapted requirements: o The IMPs are authorised; o If the IMPs are not used in accordance with the terms of the marketing authorisation, that use is supported by published scientific evidence on safety and efficacy; o Minimal additional risk or burden to the safety of the subjects compared to normal clinical practice.	• No change
• No portal		• No change
• Multiple submissions for one trial (one submission per Member State Concerned) / no harmonised dossier • Double submission within a Member State Concerned: to NCA and to Ethics Committees	• EU portal and database accessible to Member State NCAs and ECs • Single e-submission to all Member States via EU portal/harmonised dossier for one trial. E-submission of structured data and documents by Member State	• Single e-submission • For EU-funded platform trials during the pandemic, the assessment of Parts I & II involving NCAs and ECs to reach a single decision will be mandatory for all Member States
• Individual assessment by each Member State with no IT collaboration tool available / no election of a decision-	• Coordinated assessment between Reporting Member State and Member State Concerned for Part I* facilitated by	

*Part I :
Low-interventional CT; Benefits vs. risks for subjects, including relevance of CT, reliability and robustness of data; Manufacturing and importation for IMP; Labelling requirements; Investigator's Brochure.
Part II :
Informed consent, subject recruitment, data protection; Reward/compensation investigators/subjects; Suitability of investigators and of trial sites; Damage compensation; Collection/storage/use of biological samples

making Reporting Member State • No single Member State decision (NCA & ECs) • Burden to NCAs in uploading information in the system • Limited EudraCT data availability to the public: structured data from the application (CTA) and summary of results	collaboration tools • National evaluation is still required for Part II* • Up to MS to decide who is involved in Part I and Part II of the assessment (ie, NCA/EC) to reach single decision; • Single Member State decision • Distribution of the burden among users • View all CT-related information	• A protocol pre-submission review involving all relevant NCAs/ethics committees, to discuss potential grounds for non-approval early on. • EMA guidance during the health crisis, enabling the implementation of a fast-track process by offering review by Research Ethics Committee and NCA with submission of one application reviewed within 1 week. • No change

*Part I :
Low-interventional CT; Benefits vs. risks for subjects, including relevance of CT, reliability and robustness of data; Manufacturing and importation for IMP; Labelling requirements; Investigator's Brochure.
Part II :
Informed consent, subject recruitment, data protection; Reward/compensation investigators/subjects; Suitability of investigators and of trial sites; Damage compensation; Collection/storage/use of biological samples

Table 1. Assessment time for (inter)national approval for DisCoVeRy and SolidAct

DisCoVeRy

	First submission (2020)		Amendments(2021)	
Country	**EC**	**NCA**	**EC**	**NCA**
Austria	21	17	pending	pending
Belgium	15	13	28	16
Czech Republic			pending [a]	98
France	0	3	17	33
Greece			pending	pending
Hungary			27	32
Ireland			108	56
Luxembourg	17	19	28	42
Norway			49	38
Poland			pending [a]	66
Portugal	41	7	43§	67
Slovakia			pending [a]	53
Spain			87	pending
Median (IQR)	17 (15-21)	13 (7-17)	35.5 (27.75-58.5)	47.5 (34.25-63.5)

[a] Some local regulations require approval by the national competent authority before submission to the ethics committee.

SolidAct

	international		National	
Country	**VHP**	**VHP+**	**NCA**	**EC**
Austria	x		21	Pending
Belgium	x		2	Pending
Czech Republic			44	27
France	x		19	6
Germany		x	134	Pending
Greece			14	
Hungary		x	42	42
Ireland	x		3	83
Italy	x		12	
Luxembourg	x		91	36
Norway		x	5	29
Portugal		x	33	84
Slovakia	x		20	30
Spain		x	48	35
Switzerland	x			
Turkey				
Median (IQR)	20,5 (12,5-43,5)		35 (29-42)	

Contributors

AD, MT, AB, JS, CD, SLM, and MD were in charge of data curation and accessed and verified the data. AD, MT, VCS, AB, and YY wrote the original draft of the commentary, which was reviewed and edited by AD, MT, VCS, J-AR and YY. All authors contributed to refinement of and approved this manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

No author declared a conflict of interest in relation to the submitted work. JD reports grants from the EU Comission (Horizon 2020, Horizon Europe, IMI), for ECRIN, outside the submitted work. ICO reports support from EU Commission, outside the submitted work. JAP reports consulting fees, lectures fees ans support for attending meeting from Pfizer, outside the submitted work; consulting fees from MSD, Jansen-Cilag, outside the submitted work. MH reports grants from The Belgian Center for Knowledge (KCE), the Fonds Erasme-COVID-Université Libre de Bruxelles, outside the submitted work; grants from the EU-Horizon programme, outside the submitted work; support for ECCMID congress 2021 from Pfizer, outside the submitted work; Co-leader of the Belgian Guidelines on Therapeutics for COVID-19, outside the submitted work; acting as a treasurer for the Belgian Society of Clinical Microbiology and Infectious Diseases, outside the submitted work. ØM acting as a Chair of Management Board for Clinical Research initiative for Global Health (CRIGH) to facilitate international collaboration in non-commercial multicentric clinical trials, outside the submitted work. DM reports grants from Janssen for Inserm, outside the submitted work; lectures fees from Janssen and Gilead, outside the submitted work. All other authors declare no competing interests.

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